

(PCT Article 18 and Rules 43 and 44)

pplicant's or agent's file reference	FOR FURTHER see Notification of (Form PCT/ISA/2	of Transmittal of International Search Report 20) as well as, where applicable, item 5 below.
RB/P/83/W0 ternational application No.	International filing date (day/month/year)	(Earliest) Priority Date (day/month/year)
CT/GB 00/03328	31/08/2000	31/08/1999
pplicant		
RADFORD PARTICLE DESIGN		thority and is transmitted to the applicant
according to Article 18. A copy is being		
This International Search Report consis	ts of a total of4 sneets. by a copy of each prior art document cited in thi	is report.
language in which it was filed,	ne international search was carried out on the b unless otherwise indicated under this item.	
	n was carried out on the basis of a translation o).	
was carried out on the basis of	the sequence noting.	international application, the international search
contained in the intern	ational application in written form.	orm
	international application in computer readable f	om.
furnished subsequent	y to this Authority in written form.	
furnished subsequent	y to this Authority in computer readble form.	- does not go beyond the disclosure in the
	subsequently furnished written sequence listing as filed has been furnished.	
the statement that the furnished	information recorded in computer readable ion	m is identical to the written sequence listing has been
	found unsearchable (See Box I).	
3. Unity of invention is	lacking (see Box 11).	
4. With regard to the title , The text is approved a	as submitted by the applicant.	
the text has been est	ablished by this Authority to read as follows:	
With regard to the abstract,		
	as submitted by the applicant.	. B. W. The englished may
the text has been es within one month from	tablished, according to Rule 38.2(b), by this Au m the date of mailing of this international searc	thority as it appears in Box III. The applicant may, h report, submit comments to this Authority.
	e published with the abstract is Figure No.	None of the figures.
X as suggested by the		Notice of the lightes.
	ant failed to suggest a figure.	
	better characterizes the invention.	



A CLASS	SIFICATION OF SUBJECT MAT A61K9/16	TER
TPC 7	Δ61K9/16	

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols) IPC 7-A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, BIOSIS, CHEM ABS Data

	ENTS CONSIDERED TO BE RELEVANT Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Category °	Citation of document, with indicator,	
X	EP 0 852 140 A (NISSAN CHEMICAL IND LTD) 8 July 1998 (1998-07-08)	1-6, 10-16, 23,31
	column 1, line 5 - line 12 page 11 -page 12; examples 1-7	
X	WO 96 31202 A (ELAN CORP PLC) 10 October 1996 (1996-10-10) page 3, line 13 - line 16 page 7 -page 8; example 1	1-5,23, 31
X	EP 0 582 169 A (BAYER ITALIA SPA) 9 February 1994 (1994-02-09) page 3; example 1	1-5,23, 31
х	WO 92 11000 A (SANOL ARZNEI SCHWARZ GMBH) 9 July 1992 (1992-07-09) page 6 -page 7; examples 1,2	1-5,23, 31
	-/	

	l .	·
X Fur	ther documents are listed in the continuation of box C.	Patent family members are listed in annex.
'A' docum consi 'E' earlier filing 'L' docum which citati 'O' docum other	nent which may throw doubts on priority claim(s) or n is cited to establish the publication date of another on or other special reason (as specified) nent referring to an oral disclosure, use, exhibition or r means nent published prior to the international filing date but than the priority date claimed	 *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such document is combined with one or more other such documents, such combination being obvious to a person skilled in the art. *&* document member of the same patent family Date of mailing of the international search report
	e actual completion of the international search 22 February 2001	02/03/2001
Name and	d mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Authorized officer Boulois, D

1

Citation of document, with indication, where appropriate, of the relevant passages	
WO 98 13136 A (MICROENCAPSULATION CENTRE; RICHARD JOEL (FR); BENOIT JEAN PIERRE () 2 April 1998 (1998-04-02) page 1, line 4 - line 28 page 5, line 5 -page 7, line 18 page 12 -page 13; example 9	1-5,23, 31
WO 99 25322 A (CARLI FABIO ;COLOMBO ITALO (IT); ALESSI PAOLO (IT); CORTESI ANGELO) 27 May 1999 (1999-05-27) page 4 -page 5; examples 1,6	1-5,23, 31
WO 97 31691 A (UNIV KANSAS ;SUBRAMANIAM BALA (US); SAID SAID (US); RAJEWSKI ROGER) 4 September 1997 (1997-09-04) page 1, line 16 - line 26 page 15 -page 23; examples 1-4	1-5,23,
WO 95 01221 A (UNIV BRADFORD ; HANNA MAZEN (GB); YORK PETER (GB)) 12 January 1995 (1995-01-12) cited in the application page 37 -page 50; examples 5,10,16	1-5,23, 31
DEBENEDETTI P G ET AL: "APPLICATION OF SUPERCRITICAL FLUIDS FOR THE PRODUCTION OF SUSTAINED DELIVERY DEVICES" JOURNAL OF CONTROLLED RELEASE, NL, ELSEVIER SCIENCE PUBLISHERS B.V. AMSTERDAM, vol. 24, no. 1 / 03, 1 May 1993 (1993-05-01), pages 27-44, XP0003u3918 ISSN: 0168-3659 the whole document	1-5,23,
WILKINS S. ET AL: "The formation of indomethacin:polymer co-precipitates by the solution enhanced dispersion by supercritical fluids (SEDS) process" J. OF PHARMACY AND PHARMACOLOGY, vol. 51, September 1999 (1999-09), page 291 XP000905174 the whole document	1-6, 10-31
TAYLOR L. ET AL: "Spectroscopic characterization of interactions between PVP and indomethacin in amorphous molecular dispersions" PHARM. RES., vol. 14, 1997, pages 1691-1698, XP000905065 page 1691 -page 1692 page 1695	1-6, 10-23,31
	;RICHARD JOEL (FR); BENDIT JEAN PIERRE () 2 April 1998 (1998-04-02) page 1, line 4 - line 28 page 5, line 5 -page 7, line 18 page 12 -page 13; example 9 WO 99 25322 A (CARLI FABIO ;COLOMBO ITALO (IT); ALESSI PAOLO (IT); CORTESI ANGELO) 27 May 1999 (1999-05-27) page 4 -page 5; examples 1,6 WO 97 31691 A (UNIV KANSAS ;SUBRAMANIAM BALA (US); SAID SAID (US); RAJEWSKI ROGER) 4 September 1997 (1997-09-04) page 1, line 16 - line 26 page 15 -page 23; examples 1-4 WO 95 01221 A (UNIV BRADFORD ;HANNA MAZEN (GB); YORK PETER (GB)) 12 January 1995 (1995-01-12) cited in the application page 37 -page 50; examples 5,10,16 DEBENEDETTI P G ET AL: "APPLICATION OF SUPTERTICAL FLUIDS FOR THE PRODUCTION OF SUSTAINED DELIVERY DEVICES" JOURNAL OF CONTROLLED RELEASE,NL,ELSEVIER SCIENCE PUBLISHERS B.V. AMSTERDAM, vol. 24, no. 1 / 03, 1 May 1993 (1993-05-01), pages 27-44, XP0003u3918 ISSN: 0168-3659 the whole document WILKINS S. ET AL: "The formation of indomethacin:polymer co-precipitates by the solution enhanced dispersion by supercritical fluids (SEDS) process" J. OF PHARMACY AND PHARMACOLOGY, vol. 51, September 1999 (1999-09), page 291 XP000905174 the whole document TAYLOR L. ET AL: "Spectroscopic characterization of interactions between PVP and indomethacin in amorphous molecular dispersions" PHARM. RES., vol. 14, 1997, pages 1691-1698, XP000905065 page 1691 -page 1692 page 1695

C.(Continua	ation) DOCUMENTS CONSIDERED TO BE RELEVANT	Relevant to claim No.
Category °	Citation of document, with indication, where appropriate, of the relevant passages	
A	SHEKUNOV B. ET AL: "Control of Particle Morphology using solution enhanced dispersion by supercritical fluids (SEDS)" PHARM. RES., vol. 14, 1997, pages 195-196, XP000905093 the whole document	1
E	WO 01 03821 A (YORK PETER ;BRADFORD PARTICLE DESIGN PLC (GB); HANNA MAZEN HERMIZ) 18 January 2001 (2001-01-18) page 8, line 14 - line 21 page 22 -page 23; example 3	1-6, 10-23,31
X	US 4 404 183 A (KAWATA HIROITSU ET AL) 13 September 1983 (1983-09-13)	1-6, 10-16, 23,31
	claims 1,2	7,8
A	WO 97 44028 A (MERCK FROSST CANADA INC; HANCOCK BRUNO (CA); WINTERS CONRAD (CA);) 27 November 1997 (1997-11-27) the whole document	

•	inform	ation on patent family membe	rs	International A	0/03328
Patent document		, Publication		tent family	Publication
cited in search report	Ì	date	m	ember(s)	date
EP 0852140	A	08-07-1998	AU AU NO	702088 B 6669396 A 980549 A	11-02-1999 12-03-1997 02-04-1998
			NZ CA	315089 A 2228907 A	29-06-1999 27-02-1997
			CN	1192677 A	09-09-1998
			CZ WO	9800326 A 9706781 A	17-06-1998 27-02-1997
W0 9631202		 10-10-1996	IE	950233 A	16-10-1996
			AU	700612 B	07-01-1999 23-10-1996
			AU	5286696 A	10-10-1996
			CA EP	2217462 A 0818996 A	21-01-1998
			JP	11503147 T	23-03-1999
			NZ	304975 A	24-09-1998
			US	5641745 A	24-06-1997
			ZA	9602670 A	09-10-1996
EP 0582169	Α	09-02-1994	IT	1255792 B	16-11-1995 06-02-1994
			CA JP	2101680 A 7002700 A	06-01-1995
			US	5491154 A	13-02-1996
			US	5622978 A	22-04-1997
WO 9211000	Α	09-07-1992	DE	4041563 A	25-06-1992
			AT	116542 T	15-01-1995 23-06-1992
			CA	2098814 A 59104172 D	16-02-1995
			DE DK	563176 T	06-03-1995
			EP	0563176 A	06-10-1993
			ES	2067324 T	16-03-1995
		,	FΙ	932761 A	16-06-1993
			GR	3015623 T	30-06-1995
			HU	217817 B	28-04-2000
			ΙE	914313 A	01-07-1992
			JP	6504531 T	26-05-1994 01-12-1998
			KR	162105 B 99892 A,B	31-12-1992
			PT US	5424076 A	13-06-1995
WO 9813136	A	02-04-1998	FR	2753639 A	27-03-1998 15-08-2000
			AT DE	194926 T 69702666 D	31-08-2000
			EP	0930936 A	28-07-1999
			ES	2149613 T	01-11-2000
			PT	930936 T	29-12-2000
WO 9925322	Α	27-05-1999	IT	1296464 B	25-06-1999 07-06-1999
			AU BR	2153199 A 9814656 A	03-10-2000
			EP	1033977 A	13-09-2000
WO 9731691	A	04-09-1997	US	5874029 A	23-02-1999
			US	5833891 A	10-11-1998 26-08-1999
			AU	709384 B 2193697 A	16-09-1999
			AU CA	2193097 A 2247900 A	04-09-1997
			1.4	LL71300 N	J. J,

		<u> </u>)/03328 Publication
Patent document cited in search report		Publication date		tent family ember(s)	date
WO 9731691	 A		EP	0885038 A	23-12-1998
		12-01-1995	AT	174530 T	15-01-1999
WO 9501221	Α	12-01-1993	AU	677345 B	17-04-1997
			AU	7007194 A	24-01-1995
			CA	2166301 A	12-01-1995
			DE	69415320 D	28-01-1999
			DE	69415320 T	24-06-1999
			DK	706421 T	23-08-1999
			EP	0706421 A	17-04-1996
			ES	2128564 T	16-05-1999
			GR	3029612 <u>T</u>	30-06-1999
			JP	8511987 T	17-12-1996
			NZ	267697 A	26-05-1997 17-04-1998
			SG	47392 A	22-12-1998
			US 	5851453 A 	
WO 0103821	A	18-01-2001	NONE		
	A	13-09-1983	JP	1272484 C	11-07-1985
US 4404183	А	13 09 1303	JР	56133217 A	19-10-1981
			ĴΡ	59048810 B	29-11-1984
			JP	1591530 C	30-11-1990
			JP	2009007 B	28-02-1990
			JP	56049314 A	02-05-1981
			CA	1146866 A	24-05-1983 29-03-1985
			CH	648484 A	22-01-1981
			DE	3024858 A	16-11-1981
			ES	493152 D 8200557 A	01-02-1982
			ES ES	499854 D	01-06-1982
			ES	8205125 A	16-09-1982
			FR	2460667 A	30-01-1981
			FR	2489146 A	05-03-1982
			GB	2053681 A,B	11-02-1981
			ΙT	1132169 B	25-06-1986
			SE	448342 B	16-02-1987
			SE	8004938 A	06-01-1981
			US	4343789 A	10-08-1982 16-06-1987
			US 	4673564 A 	
WO 9744028	A	27-11-1997	AU	3004997 A	09-12-1997 30-09-1999
			BG	103000 A 9709097 A	03-08-1999
			BR CZ	9803738 A	16-06-1999
			EP	0910368 A	28-04-1999
			HR	970262 A	30-06-1998
			JP	11512754 T	02-11-1999
			NO.	985342 A	16-11-1998
			PL	329940 A	26-04-1999
			SK	156798 A	18-01-200
			TR	9802345 T	22-03-199 ⁶ 16-05-200
			US 	6063811 A	10-05-200



From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

Commissioner **US Department of Commerce** United States Patent and Trademark Office, PCT 2011 South Clark Place Room CP2/5C24 Arlington, VA 22202

ETATS-UNIS D'AMERIQUE 19 June 2001 (19.06.01)

Date of mailing (day/month/year) in its capacity as elected Office Applicant's or agent's file reference International application No. ARB/P/83/WO PCT/GB00/03328 Priority date (day/month/year) International filing date (day/month/year) 31 August 1999 (31.08.99) 31 August 2000 (31.08.00) **Applicant** YORK, Peter et al

	YORK, Peter et al
1.	The designated Office is hereby notified of its election made: X in the demand filed with the International Preliminary Examining Authority on: 26 March 2001 (26.03.01)
	in a notice effecting later election filed with the International Bureau on:
2.	The election X was was not was not made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bur au of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland

Authorized officer

Zakaria EL KHODARY

Telephone No.: (41-22) 338.83.38

Facsimile No.: (41-22) 740.14.35

Copy for the Elected Office (EO/US)







PCT

NOTIFICATION OF THE RECORDING **OF A CHANGE**

BREWSTER, Andrea, Ruth Greaves Brewster

From the INTERNATIONAL BUREAU

(PCT Rule 92bis.1 and Administrative Instructions, Section 422) Date of mailing (day/month/year) 27 October 2001 (27.10.01)	24A Woodborough Road Winscombe North Somerset BS25 1AD ROYAUME-UNI		
Applicant's or agent's file reference ARB/P/83/WO	IMPORTANT NOTIFICATION		
International application No. PCT/GB00/03328	International filing date (day/month/year) 31 August 2000 (31.08.00)		
The following indications appeared on record concerning: The following indications appeared on record concerning: the applicant the inventor	the agent the common representative State of Nationality State of Residence		
Name and Address BRADFORD PARTICLE DESIGN PLC Unit 69 Listerhills Science Park Campus Road Bradford BD7 1HR United Kingdom	GB GB Telephone No.		
The International Bureau hereby notifies the applicant that the person	Teleprinter No. the following change has been recorded concerning: dress the nationality the residence		
Name and Address BRADFORD PARTICLE DESIGN LIMITED Unit 69 Listerhills Science Park Campus Road Bradford BD7 1HR United Kingdom	State of Nationality GB GB Telephone No. Facsimile No. Teleprinter No.		
3. Further observations, if necessary:			
4. A copy of this notification has been sent to: X the receiving Office the International Searching Authority X the International Preliminary Examining Authority	the designated Offices concerned X the elected Offices concerned other:		
The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer R. Raissi Telephone No.: (41-22) 338.83.38		
Facsimile No.: (41-22) 740.14.35	· viegnama i i i i i i i i i i i i i i i i i i		

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference ARB/P/83/WO	FOR FURTHER ACTI	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)		
	International filing date (day)	/month/vear)	Priority date (day/month/year)	
International application No.	31/08/2000	,	31/08/1999	
PCT/GB00/03328				
International Patent Classification (IPC) or A61K9/00	national classification and IPC			
Applicant				
BRADFORD PARTICLE DESIGN	I PLC et al.			
This international preliminary examples and is transmitted to the application.	amination report has been pront according to Article 36.	epared by this inte	ernational Preliminary Examining Authority	
2. This REPORT consists of a total	l of 8 sheets, including this c	over sheet.		
been amonded and are the	nied by ANNEXES, i.e. shee basis for this report and/or sh n 607 of the Administrative In	leels containing is	on, claims and/or drawings which have ectifications made before this Authority he PCT).	
These annexes consist of a total	al of sheets.			
3. This report contains indications	relating to the following items	s:		
ι ⊠ Basis of the report				
II □ Priority		ti i i i i i i i i i i i i i i i i i i	o and industrial applicability	
	of opinion with regard to nov	elty, inventive ste	p and industrial applicability	
IV Lack of unity of inv	ention	de analysis	ventive step or industrial applicability:	
V 🗵 Reasoned stateme citations and expla	ent under Article 35(2) with re- inations suporting such stater	gard to novelly, in ment	ventive step or industrial applicability;	
VI 🛛 Certain document				
	the international application			
VIII 🛛 Certain observatio	ns on the international applic	ation		
1				
		Data of completion	of this report	
Date of submission of the demand		Date of completion	of this report	
Date of submission of the demand 26/03/2001		Date of completion	of this report	
26/03/2001 Name and mailing address of the intermoreliminary examining authority:			of this report	
26/03/2001 Name and mailing address of the interm	P.B. 5818 Patentlaan 2 ys Bas	13.11.2001	of this report	



I. Basis	of the	report
----------	--------	--------

1.	With regard to the elements of the international application (Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17)): Description, pages:							
	1-37, <i>F</i> 39	\1-A13,38,	as originally filed					
	Claim	ns, No.:						
	1-31		as originally filed					
	Draw	ings, sheets:						
	1/21-	21/21	as originally filed					
2	. With	With regard to the language , all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.						
			available or furnished to this Authority in the following language: , which is:					
		the language of	a translation furnished for the purposes of the international search (under Rule 23.1(b)).					
		the lenguege of	publication of the international application (under Rule 48.3(b)).					
		the language of 55.2 and/or 55.3	a translation furnished for the purposes of international preliminary examination (under hule					
;	3. With inter		ucleotide and/or amino acid sequence disclosed in the international application, the ary examination was carried out on the basis of the sequence listing:					
		contained in the	international application in written form.					
		filed together wi	th the international application in computer readable form.					
		furnished subse	quently to this Authority in written form.					
		furnished subse	quently to this Authority in computer readable form.					
		the international	hat the subsequently furnished written sequence listing does not go beyond the disclosure in application as filed has been furnished.					
		The statement listing has been	that the information recorded in computer readable form is identical to the written sequence					
	4. The	e amendments h	ave resulted in the cancellation of:					
		the description	pages:					



Nos.: ☐ the claims, sheets: □ the drawings,
 □ This report has been established as if (some of) the amendments had not been made, since they have been 5. 🗆 considered to go beyond the disclosure as filed (Rule 70.2(c)): (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary: see separate sheet

- V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- 1. Statement

Novelty (N)

Yes: No:

Claims 7-9,17-20,29,30

Claims 1-6,10-16,21-28,31

Inventive step (IS)

Yes:

Claims

No:

Claims 1-31

Industrial applicability (IA)

Yes:

Claims 1-31

Claims No:

2. Citations and explanations see separate sheet

Certain documents cited VI.

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted: see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:



see separate sheet

EXAMINATION REPORT - SEPARATE SHEET

R Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Reference is made to the following documents:

D1: EP-A-852140

D2: WO-A-9631202

D3: EP-A-582169

D4: WO-A-9211000

D5: WO-A-9813136

D6: WO-A-9925322

D7: WO-A-9731691

D8: WO-A-9501221 (cited in the application)

D9: J. Controlled Release, 24(1993), 27-44

D10: Pharm. Res., 14(12),1691-8

D11: US-A-4404183

2. The present application does not satisfy the criterion set forth in Article 33(2) PCT because the subject-matter of Claims 1-6,10-16,21-28,31 is not new in respect of prior art as defined in the regulations (Rule 64(1)-(3) PCT).

For the judgement of novelty of the present application, it appeared that the concepts of "coformulation" and *stable" must be interpretated widely and not only in the light of the explanations given in the description. It appears moreover that the term "stable" has not a very clear definition in the present application, even with the explanations given on page 3, lines 1-9, since it is impossible to know which percentages are meant.

It was also considered that any "coformulation" obtained by a process allowing the formulation of a drug in amorphous drug, would fulffil the stability requirements of the claims.

Lack of novelty of the following claims is stated agaisnt the disclosure of the following documents:

- lack of novelty of claims 1-6,10-16,23,31 over D1 (see D1, col. 1, l. 5-12; page 11-12, examples 1-7)
- lack of novelty of claims 1-5,23,31 over D2 (see D2, p. 3, l. 13-16; p. 7,8, example 1)

- lack of novelty of claims 1-5,23,31 over D3 (see D3, page 3, example 1) - lack of novelty of claims 1-5,23,31 over D4 (see D4, pages 5-7, examples 1,2)
- lack of novelty of claims 1-5,23,31 over D5 (see D5, p. 1, l. 4-28; p. 5, l. 5-p. 7, l. 18; p.12-13, example 9)
- lack of novelty of claims 1-5,23,31 over D6 (see D6, p. 4,5, examples 1,6)
- lack of novelty of claims 1-5,23,31 over D7 (see D7, p. 1, l. 16-26; p. 15-23, examples
- lack of novelty of claims 1-5,23,31 over D8 (see D8, p. 37-50, examples 5,10,16)
- lack of novelty of claims 1-5,23,31 over D9
- lack of novelty of claims 2-6, 10-16, 21-28, 31 over D10 (see D10, p. 1691,2,5)
- lack of novelty of claims 1-6,10-16,23,31 over D11 (see D11, claims 1,2)
- 3. The documents D1, D2, D3, D4, D5, D6, D7, D8, D9, D10, D11 appear to be of particular relevance as far as inventive step is concerned (Article 33(3) PCT). These documents solve indeed the same problem, namely making a coformulation of an active in amorphous state, so that, as far as novel subject-matter is concerned, the present application does apparently not fulfill the requirements of Article 33(3) PCT over these prior art documents.

It seems in particular to be a normal design option to use the same concept for a specific drug.

It also pointed out that the introduction of a disclaimer in an independent claim does not restore the inventive step of the said claim.

Therefore, as no unexpected effect for the present composition (as far as novel) over the prior art compositions has been demonstrated, this composition does apparently not fulfill the requirements of Article 33(3) PCT.

Re Item VI

Certain documents cited

Certain published documents (Rule 70.10)

Application No Patent No

Publication date(day/month/year)

Filing date(day/month/year)

Priority date (day/month/year)

INTERNATIONAL PRELIMINARY **EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/GB00/03328

WO-A-0103821(E1) 18.1.2001

7.7.2000

7.7.1999

Non-written disclosures (Rule 70.9)

Kind of non-written disclosure

Date of non-written disclosure(day/month/year) Date of written disclosure(day/month/year)

J. of Pharm. Pharmacol.,51,sept. 1999,291 (E2)

sept. 1999

The document E1 will be taken in consideration in the regional phase for the judgement of novelty of claims 1-6,10-23,31 (see E1, page 8, I. 14-21; p. 22-23, example 3).

The content of document E2 may also be relevant for the novelty of claims 1-6,10-31 (see the whole document.

Re Item VII

Certain defects in the international application

Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in the documents D1,D2,D3,D4,D5,D6,D7,D9,D10 and D11 is not mentioned in the description, nor are these documents identified therein.

Re Item VIII

Certain observations on the international application

- 1. It is clear from the description that the process of preparation of claim 26 is essential to the definition of the invention.
- Since independent claims 1,2 10, 17 do not contain this feature they do not meet the requirement following from Article 6 PCT taken in combination with Rule 6.3(b) PCT that any independent claim must contain all the technical features essential to the definition of the invention.
- 2. The present application does not meet the requirements of Article 6 PCT because claims 24,25 and 27 are not clear.
- It appears from the description on page 1, lines 6-12 that the SEDS process exists in modified versions, and therefore that the term does not have a precise and recognized

meaning.

3. The term "COX-2 selective inhibitor" as used in the present dependent claims 7 and 8 defines the active agent by its pharmacological profile, nameyl its affinity to a enzyme. However, a compound cannot be sufficiently characterised by its pharmacological profile or its mode of action as it is done by an expression like ""COX-2 selective inhibitor"because it is difficult to know which substances are encompassed in this expression. Moreover, the definition of an "inhibitor" is also not clear.

For instance it is highly credible that sulfuric acid or sodium hydroxide would also be ""COX-2 selective inhibitor". It is also not clear at which level of affinity a compound can be defined as an inhibitor (or as an agonist). A lot of compounds have indeed both activities depending on the concentration used.

Thus the present dependent claims 7 and 8 are not clear, because the pharmacological definition is vague and renders thus the scope of said claims obscure (Article 6 PCT).

(19) World Intellectual Property Organization International Bureau



HARRE BUILDUR II BURIN BEIRK HAR I IN SAL HARD BAHR BUIL BHAR BURIN HAR BURIN HAR BURIN HAR

(43) International Publication Date 8 March 2001 (08.03.2001)

PCT

(10) International Publication Number WO 01/15664 A3

(51) International Patent Classification7:

A61K 9/16

(21) International Application Number: PCT/GB00/03328

(22) International Filing Date: 31 August 2000 (31.08.2000)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data: 9920558.5

31 August 1999 (31.08.1999) GB

(71) Applicants (for all designated States except US): BRAD-FORD PARTICLE DESIGN PLC [GB/GB]; Unit 69 Listerhills Science Park, Campus Road, Bradford BD7 1HR (GB). BRISTOL-MYERS SQUIBB COMPANY [US/US]; P.O. Box 4000, Princetown, NJ 08543-4000 (US)

(72) Inventors; and

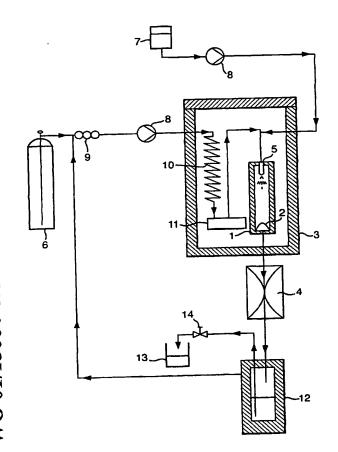
(75) Inventors/Applicants (for US only): YORK, Peter [GB/GB]; 47 Parish Ghyll Drive, Ilkley LS29 9PR (GB). WILKINS, Simon, Anthony [GB/GB]; 8 Beckbury Street, Farsley, Leeds LS28 5BP (GB). STOREY, Richard, Anthony [GB/GB]; 18 Laurel Way, Chartham, Canterbury, Kent CT4 7TJ (GB). WALKER, Stephen, Ernest [GB/GB]; Roundwood Grange, Roundwood Road, Baildon, Shipley, West Yorkshire BD17 7JX (GB). HARLAND, Ronald, Scott [US/US]; 1 Harlow Court, Yardley, PA 19067 (US).

(74) Agents: BREWSTER, Andrea, Ruth et al.; Greaves Brewster, 24A Woodborough Road, Winscombe, North Somerset BS25 1AD (GB).

(81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,

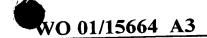
[Continued on next page]

(54) Title: COFORMULATION METHODS AND THEIR PRODUCTS



(57) Abstract: A coformulation of an active (preferably pharmaceutically active, for instance a COX-2 enzyme inhibitor) substance and an oligomeric or polymeric excipient, containing at least 10 % of the active, between 80 and 100 % of which is amorphous. The amorphous phase is stable, with respect to the crystalline phase(s), for at least theree months after its preparation when stored at between O and 10 °C. The invention also provides processes, preferably involving SEDSTM particle formation, for preparing such a coformulation.

WO 01/15664 A3





- LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.
- (84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:

- with international search report
- (88) Date of publication of the international search report: 20 September 2001

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

A. CLASSIFICATION OF SUBJECT MATTER IPC 7 A61K9/16

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols) A61K IPC 7

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

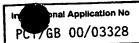
EPO-Internal, WPI Data, PAJ, BIOSIS, CHEM ABS Data

. DOCUME	NTS CONSIDERED TO BE RELEVANT Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
ategory °	Citation of document, with indication, where appropriate, and	
(EP 0 852 140 A (NISSAN CHEMICAL IND LTD) 8 July 1998 (1998-07-08)	1-6, 10-16, 23,31
	column 1, line 5 - line 12 page 11 -page 12; examples 1-7	. 5.00
X	WO 96 31202 A (ELAN CORP PLC) 10 October 1996 (1996-10-10) page 3, line 13 - line 16 page 7 -page 8; example 1	1-5,23, 31
X	EP 0 582 169 A (BAYER ITALIA SPA) 9 February 1994 (1994-02-09) page 3; example 1	1-5,23, 31
X	WO 92 11000 A (SANOL ARZNEI SCHWARZ GMBH) 9 July 1992 (1992-07-09) page 6 -page 7; examples 1,2	1-5,23, 31
	-/	

Y Further documents are listed in the continuation of box C.	Patent family members are listed in annex.
Special categories of cited documents: 'A' document defining the general state of the art which is not considered to be of particular relevance 'E' earlier document but published on or after the international filing date 'L' document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) 'O' document referring to an oral disclosure, use, exhibition or other means 'P' document published prior to the international filing date but later than the priority date claimed	*T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art. *&* document member of the same patent family Date of mailing of the international search report
Date of the actual completion of the international search	02/03/2001
22 February 2001	Authorized officer
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Boulois, D

7

1



		PCT/GB 00/03328
	tion) DOCUMENTS CONSIDERED TO BE RELEVANT	
Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 98 13136 A (MICROENCAPSULATION CENTRE; RICHARD JOEL (FR); BENOIT JEAN PIERRE () 2 April 1998 (1998-04-02) page 1, line 4 - line 28 page 5, line 5 -page 7, line 18 page 12 -page 13; example 9	1-5,23, 31
X	WO 99 25322 A (CARLI FABIO ;COLOMBO ITALO (IT); ALESSI PAOLO (IT); CORTESI ANGELO) 27 May 1999 (1999-05-27) page 4 -page 5; examples 1,6	1-5,23,
X	WO 97 31691 A (UNIV KANSAS ;SUBRAMANIAM BALA (US); SAID SAID (US); RAJEWSKI ROGER) 4 September 1997 (1997-09-04) page 1, line 16 - line 26 page 15 -page 23; examples 1-4	1-5,23,
X	WO 95 01221 A (UNIV BRADFORD ;HANNA MAZEN (GB); YORK PETER (GB)) 12 January 1995 (1995-01-12) cited in the application page 37 -page 50; examples 5,10,16	1-5,23,
x	DEBENEDETTI P G ET AL: "APPLICATION OF SUPERCRITICAL FLUIDS FOR THE PRODUCTION OF SUSTAINED DELIVERY DEVICES" JOURNAL OF CONTROLLED RELEASE, NL, ELSEVIER SCIENCE PUBLISHERS B.V. AMSTERDAM, vol. 24, no. 1 / 03, 1 May 1993 (1993-05-01), pages 27-44, XP000303918 ISSN: 0168-3659 the whole document	1-5,23,
P,X	WILKINS S. ET AL: "The formation of indomethacin:polymer co-precipitates by the solution enhanced dispersion by supercritical fluids (SEDS) process" J. OF PHARMACY AND PHARMACOLOGY, vol. 51, September 1999 (1999-09), page 291 XP000905174 the whole document	1-6, 10-31
X	TAYLOR L. ET AL: "Spectroscopic characterization of interactions between PVP and indomethacin in amorphous molecular dispersions" PHARM. RES., vol. 14, 1997, pages 1691-1698, XP000905065 page 1691 -page 1692 page 1695	1-6, 10-23,31

int an all Application No
PC 17 GB 00/03328

		PC 17 GB 00/03328
C.(Continue	ation) DOCUMENTS CONSIDERED TO BE RELEVANT	
Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	SHEKUNOV B. ET AL: "Control of Particle Morphology using solution enhanced dispersion by supercritical fluids (SEDS)" PHARM. RES., vol. 14, 1997, pages 195-196, XP000905093 the whole document	1
E	WO 01 03821 A (YORK PETER ;BRADFORD PARTICLE DESIGN PLC (GB); HANNA MAZEN HERMIZ) 18 January 2001 (2001-01-18) page 8, line 14 - line 21 page 22 -page 23; example 3	1-6, 10-23,31
X	US 4 404 183 A (KAWATA HIROITSU ET AL) 13 September 1983 (1983-09-13)	1-6, 10-16, 23,31
	claims 1,2	
A	WO 97 44028 A (MERCK FROSST CANADA INC; HANCOCK BRUNO (CA); WINTERS CONRAD (CA);) 27 November 1997 (1997-11-27) the whole document	7,8
	·	

n on patent family members

PC GB 00/03328

		1		TCT/GB C	0, 00020
Patent document cited in search report		Publication date		tent family ember(s)	Publication date
EP 0852140	A	08-07-1998	AU	702088 B 6669396 A	11-02-1999 12-03-1997
			AU	980549 A	02-04-1998
			NO	315089 A	29-06-1999
			NZ	2228907 A	27-02-1997
			CA		09-09-1998
			CN	1192677 A	17-06-1998
			CZ	9800326 A 9706781 A	27-02-1997
			WO	9/00/81 A	
WO 9631202	Α	10-10-1996	ΙE	950233 A	16-10-1996 07-01-1999
			AU	700612 B	23-10-1996
			AU	5286696 A	10-10-1996
			CA	2217462 A	21-01-1998
			EP	0818996 A 11503147 T	23-03-1999
			JP		24-09-1998
			NZ	304975 A	24-09-1998
			US	5641745 A	09-10-1996
			ZA 	9602670 A 	
EP 0582169	A	09-02-1994	IT	1255792 B	16-11-1995
[0302103	••		CA	2101680 A	06-02-1994
			JP	7002700 A	06-01-1995
			บร	5491154 A	13-02-1996
			US	5622978 A	22-04-1997
UO 0211000		09-07-1992	DE	4041563 A	25-06-1992
WO 9211000	^	05 07 1551	AT	116542 T	15-01-1995
			CA	2098814 A	23-06-1992
			DE	59104172 D	16-02-1995
			DK	563176 T	06-03-1995
			EP	0563176 A	06-10-1993
			ES	2067324 T	16-03-1995
			FI	932761 A	16-06-1993
			GR	3015623 T	30-06-1995
			HU	217817 B	28-04-2000
			IE	914313 A	01-07-1992
			JP	6504531 T	26-05-1994
			KR	162105 B	01-12-1998
			PT	99892 A,B	31-12-1992
			ÜŚ	5424076 A	13-06-1995
		02-04-1998	FR	2753639 A	27-03-1998
WO 9813136	Α	02-04 1990	AT	194926 T	15-08-2000
			DE	69702666 D	31-08-2000
			EP	0930936 A	28-07-1999
			ES	2149613 T	01-11-2000
			PT	930936 T	29-12-2000
		 27-05-1999	IT	1296464 B	25-06-1999
WO 9925322	Α	Z1-00-1333	ĀŪ	2153199 A	07-06-1999
			BR	9814656 A	03-10-2000
			EP	1033977 A	13-09-2000
		04-09-1997	 US	5874029 A	23-02-1999
WO 9731691	Α	04-03-133/	US	5833891 A	10-11-1998
			AU	709384 B	26-08-1999
			ΛU	, 55557 6	
				2193697 A	16-09-1997
			AU CA	2193697 A 2247900 A	16-09-1997 04-09-1997

on on patent family members

In conal Application No
PCT/GB 00/03328

	tent document in search report		Publication date		ntent family nember(s)	date
WO	9731691	Α		EP	0885038 A	23-12-1998
	9501221	A	12-01-1995	AT AU CA DE DK EP ES GR JP NZ SG	174530 T 677345 B 7007194 A 2166301 A 69415320 D 69415320 T 706421 T 0706421 A 2128564 T 3029612 T 8511987 T 267697 A 47392 A	15-01-1999 17-04-1997 24-01-1995 12-01-1995 28-01-1999 24-06-1999 23-08-1999 17-04-1996 16-05-1999 30-06-1999 17-12-1996 26-05-1997 17-04-1998
				US 	5851453 A	22-12-1998
WO	0103821	Α	18-01-2001	NONE		
US	4404183	A	13-09-1983	JP JP JP JP CH DE ES ES FR GB TE US	1272484 C 56133217 A 59048810 B 1591530 C 2009007 B 56049314 A 1146866 A 648484 A 3024858 A 493152 D 8200557 A 499854 D 8205125 A 2460667 A 2489146 A 2053681 A,B 1132169 B 448342 B 8004938 A 4343789 A 4673564 A	11-07-1985 19-10-1981 29-11-1984 30-11-1990 28-02-1990 02-05-1981 24-05-1983 29-03-1985 22-01-1981 16-11-1981 01-02-1982 01-06-1982 30-01-1981 05-03-1982 11-02-1981 25-06-1986 16-02-1987 06-01-1981
WC	9744028	A	27-11-1997	AU BG BR CZ EP HR JP NO PL SK TR US	3004997 A 103000 A 9709097 A 9803738 A 0910368 A 970262 A 11512754 T 985342 A 329940 A 156798 A 9802345 T 6063811 A	09-12-1997 30-09-1999 03-08-1999 16-06-1999 28-04-1999 30-06-1999 16-11-1999 26-04-1999 18-01-2000 22-03-1999